REMARKS

Entry of the foregoing and favorable reconsideration of the subject-application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in the light of the Remarks which follow, are respectfully requested.

By way of response, claims 21, 30, 31, 32, 36, 40, 43, 50, 53, 54, 57 to 60, 64 and 65 have been amended. These amendments are made, as discussed later, to clarify the claimed subject-matter. No new matter is presented. Claims 21, 23, 30 to 34, 36, and 40 to 65 are pending.

Oath / Declaration

Please find enclosed a new declaration in compliance with 37 CFR 1.67(a) that was signed by the inventors in December 2001, and in which the citizenship of each inventor is identified.

Claims Rejections – 35 U.S.C. § 112, first paragraph

Claims 23, 30-32, 53 and 65 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to the skilled artisan that the inventors had possession of the claimed invention at the time the application was filed.

This rejection is respectfully being traversed.

The Examiner first considers that the recitation "a Survival Motor Neuron disorder" (claims 30-32 & 65) has no proper antecedent basis nor conception in context with that described within the specification at the time of filing of the application, and thereby constitutes new matter. Applicants however respectfully submit that considerations about motor neuron disorders can be

found all over the specification (at least at page 4, third paragraph, in the paragraph bridging pages 4 and 5, at page 6, paragraph 2, and so on), as well as the recitation of the fact that these disorders or diseases are due to defects in the Survival Motor Neuron gene (see, for example, page 7, second paragraph). Applicants hence believe that the specification as filed contains proper antecedent basis for "a Survival Motor Neuron disorder". Moreover, Applicants respectfully draw the Examiner's attention to the fact that the problem of new matter is not a reason for a rejection under 35 U.S.C. 112, first paragraph.

The Examiner has also rejected claims 23 and 53 because the reference to SEQ ID NO:21 in these claims allegedly constitutes new matter. As mentioned above, this should not constitute a reason for a rejection under 35 U.S.C. 112, first paragraph.

However, Applicants have amended Claim 53 by changing "SEQ ID NO:21" into "SEQ ID NO:22", hence rendering the rejection moot for the following reason : Claim 53 corresponds to former claim 22, which recited "a probe according to claim 12". Claim 12 as initially filed referred to the nucleotide sequence of Claim 10, which itself pertained to "an isolated nucleotide sequence, comprising at least around 9 nucleotides within a sequence of Claim 3 or hybridizing in stringent conditions with a sequence of any of Claims 1 to 9". Since Claim 3 pertains to a human SMN gene T-BCD541, the sequence of which is SEQ ID No:22, support for a nucleotide sequence, comprising at least 9 nucleotides within a sequence of SEQ ID No:22 exists in the application as initially filed, as reflected in the multi-dependencies of the initially filed claim.

In conclusion, Applicants deem that the presently claimed invention is supported in the specification as filed. Therefore, withdrawal of this rejection is respectfully requested.

Claims 21, 23, 30-34, 36, 40-52 and 53-65 were rejected under 35 U.S.C. § 112, first paragraph. In rendering this rejection, the Examiner purports that the specification allegedly does not reasonably provide enablement for a generic method that does not identify the specific disease state being detected. However we would like to point out to the Examiner that claims 21, 23, 53 and 64-65 pertain to kits and not to methods. Moreover this rejection is partly rendered moot by claim amendments and is being partly traversed.

The Examiner has maintained in this rejection that the term "defect" recited in claims 30 and 31, is not properly defined in the specification. In response, these claims have been amended by replacing this term with the phrase "truncation, deletion or mutation". Support for this amendment can be found throughout the specification, and for example at least on page 6, paragraphs 2 ("..., a truncated or mutated version of the SMN gene ...") and 5 ("... by partial or total deletion, by mutation or any other modification, ..."). For consistency, and to avoid a new rejection due to the word "defect", the same amendments has been made in claims 21, 53, 64 and 65, which pertain to kits.

The Examiner has also objected to the recitation of "at least one of said primers is contained within the sequence...". Claim 30 has been amended to recite that both primers are in the sequence of nucleotides 921 to 1469 of SEQ ID No:12, hence rendering the rejection moot. For the same reason as mentioned above, the same amendment has been made to claims 21, 53, 64 and 65, which pertain to kits.

The Examiner also rejects claims 40 and 50 because SEQ ID No:21 is the amino acid sequence of mouse SMN. These claims, as well as claims 36, 53, 54 and 57 to 60, have been amended by changing "SEQ ID NO:21" into "SEQ ID NO:22", corresponds to the nucleotide sequence of the entire

human SMN gene including the introns and exons, as represented on Figure 10.

Applicants believe that the above-described amendments to the claims render the rejection moot, since the specification clearly identifies the T-BCD541 gene as being the normal SMN gene, and the comparison of a DNA sample to a reference sequence, using, for example, primers or probes which are contained within said reference sequence, is only routine and does not constitute undue experimentation.

It should be recalled at this point that the ultimate question in an enablement issue is whether or not the specification contains a sufficiently explicit disclosure to enable one skilled in the art to produce the invention without the exercise of undue experimentation. As stated in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int 1986):

> "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention."

Applicants submit in view of the high level of skill and the knowledge of the art at the time this invention was filed, that it would not be undue experimentation for the skilled artisan to compare a DNA sample to a reference sequence using the primers or probes that are identified in the present specification which provides the guidance.

Furthermore, the Federal Circuit held the following position with respect to the Examiner's burden unless rendering an enablement rejection:

> "When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to scope of enablement. If the PTO meets this burden, the burden then shifts to the applicant to provide suitable proofs indicating that the specification is indeed enabling."

However, the Examiner has not provided sufficient reasons for doubting that the present methods do in fact work. Therefore, it appears that the Examiner has not met the required legal burden.

Thus, in view of the above, withdrawal of this rejection is respectfully requested.

Claims Rejections – 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 40 to 52 under 35 U.S.C. 112, second paragraph, as being indefinite because the nucleotide positions of exons 7 and 8 were not clearly identified. This rejection is obviated by the amendment to the claims. More specifically, claims 40 and 50 have been amended, by reciting the nucleotide positions of these exons. The support for this amendment is found at least on page 19, third paragraph, and in Figure 3B.

The Examiner has rejected claims 30-32, 36, 48 and 65 under 35 U.S.C. 112, second paragraph, because the metes and bounds that define SSCP are allegedly not recited. Applicants respectfully disagree, and this rejection is partly traversed and partly obviated by claim amendment. The Examiner considers that example 10 constitutes but an "example" of SSCP using different primers and DNA, and does not define what constitutes SSCP as

claimed. Applicants respectfully submit that following the amendment of claims 30 and 53, the primers used for SSCP according to these claims are defined as being contained in the sequence of nucleotides 921 to 1469 of SEQ ID No:12, which seems to be a sufficient indication for the skilled artisan to determine whether a primer corresponds or not to the primers recited in these claims. The teaching of Example 10 further defines what SSCP is, since it enumerates the steps and the reagents that are used for performing SSCP analysis. Applicants respectfully submit that these indications are sufficient for the skilled artisan to know if a method is or is not within the scope of these claims. Claim 32 has also been amended for clarification, by reciting that only step (c) is replaced by a digestion by Bsr-1.

Withdrawal of this rejection is hence respectfully submitted.

Claims 30-33, 36 and 65 have been rejected under 35 U.S.C. 112, second paragraph, as allegedly omitting essential steps. This rejection is obviated in part by the claim amendment and is being traversed-in-part. The Examiner particularly asks for clarification of the metes and bounds that constitute a "defect" or "the presence or absence of AMC/SMA". As mentioned above the term "defect" has been replaced by the phrase "truncation, deletion or mutation". Concerning "the presence or absence of AMC/SMA", Applicants respectfully submit that : (i) it is clear from the specification that alterations in the SMN gene are related to diseases such as SMA (see, for example, page 28) and AMC (see, for example, pages 36 to 38); (ii) the wild-type sequence of the SMN gene is disclosed in the specification; and (iii) the claimed methods include analysis steps (by SSCP in claims 30, 31, 36 and 65, by enzyme restriction in claim 32, and by probe hybridizing in claims 33-34). Applicants submit that it is perfectly clear for the skilled artisan that the presently claimed methods use analysis means to determine if the SMN gene is altered or not (having regard to the normal gene), thereby determining the presence or absence of the above-mentioned diseases, i.e., whether one has the disease or not.

Therefore in view of the above, withdrawal of this rejection is respectfully requested.

The Examiner has rejected claims 23, 33-34 and 53 under 35 U.S.C. 112, second paragraph, as purportedly being indefinite because the metes and bounds entailed by "stringent hybridization conditions" are allegedly unclear. This rejection is respectfully being traversed.

The Examiner considers that the Applicant's arguments in the last response are moot because a reference to Sambrook cannot constitute an incorporation by reference since Sambrook is not a US patent. Applicants however respectfully submit that the reference to Sambrook has nothing to do with an incorporation by reference. This issue here is to know whether a skilled artisan at the filing date of the present application could determine stringent conditions. Sambrook et al. indeed is but one example, but the skilled artisan could in fact determine stringent conditions depending on the length of the probe, its GC/AT content, etc. This was well known in the art at the time of filing of the present application. Moreover, Applicants point out that claim 23 does not mention stringent conditions.

From the above, withdrawal of the rejection is respectfully requested.

The Examiner has rejected claims 21, 43, 47-48 and 64 under 35 U.S.C. 112, second paragraph, because the metes and bounds entailed by "an amplification reaction" were allegedly incompletely recited, and because the term "analyzing" is allegedly unclear. This rejection is partly obviated by the claim amendment and partly traversed. Claims 21 and 64 have been clarified to recite "reagents for amplifying DNA with primers" which should render this rejection moot as it pertains to these claims.

Concerning claims 43, 47 and 48, Applicants submit that these claims are dependent on claim 40, for which the Examiner has accepted the arguments presented in the last response. Hence, Applicants submit that the same

arguments are incorporated herein and that for consistency purposes, this rejection should not be maintained. Therefore, withdrawal of the rejection is earnestly requested.

The Examiner has also rejected claim 31 under U.S.C. 112, second paragraph, as containing a recitation of "said motor neuron disorder" without proper antecedent basis. However, this claim does not contain such a recitation, and the rejection is therefore inappropriate.

Claims 23 and 40-63 have been rejected under 35 U.S.C. 112, second paragraph, because SEQ ID No:21 is an amino acid sequence. The amendment of claims 40, 50, 53, 54 and 57 to 60, by changing "SEQ ID NO:21" into "SEQ ID NO:22", renders this rejection moot.

Accordingly, withdrawal of the rejection is requested.

From the foregoing, favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition for a two (2) month extension of time for filing a reply in connection with the present application, and the required fee of $400.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, Ph.D. (Reg. No. 40,069) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachment: Version with Markings to Show Changes Made

MARKED-UP CLAIMS

21. (Twice Amended) A kit for the *in vitro* detection of a ~~defect~~ truncation, a deletion or a mutation in the survival motor neuron gene, comprising:

a set of primers wherein ~~at least one of~~ said primers ~~is~~ are contained within the sequence of nucleotides 921 to 1469 of SEQ ID No: 12;

reagents for ~~an amplification reaction~~amplifying DNA with said primers; and

a probe for the detection of the amplified product.

30. (Twice Amended) A method for detecting a truncation, a deletion or a mutation ~~defect~~ in the Survival Motor Neuron gene, said method comprising:

(a) extracting DNA from a patient sample;

(b) amplifying said DNA with primers, wherein ~~at least one of~~ said primers ~~is~~ are contained in the sequence of nucleotides 921 to 1469 of SEQ ID No: 12;

(c) subjecting said amplified DNA to a Single-Strand Conformation Polymorphism (SSCP) analysis; and

(d) detecting the presence or absence of said truncation, deletion or mutation ~~defect~~ in the Survival Motor Neuron gene, wherein the presence of said truncation, deletion or mutation ~~defect~~ is indicative of a Survival Motor Neuron disorder.

31. (Twice Amended) The method of Claim 30, wherein said detection of a truncation, deletion or mutation ~~defect~~ in the Survival Motor Neuron gene is indicative of a Spinal Muscular Atrophy.

32. (Once Amended) The method of Claim 30, wherein steps (c) ~~and (d) are~~ is replaced with a step of digestion with a *Bsr-1* enzyme.

36. (Twice Amended) A method for detecting Arthrogryposis Multiplex Congenita (AMC), said method comprising :

(a) extracting DNA from a patient sample;

(b) amplifying said DNA via a polymerase chain reaction (PCR) using unlabeled primers from exon 7 or exon 8 of the Survival Motor Neuron (SMN) gene of SEQ ID No:~~21~~22;

(c) subjecting said amplified DNA to a Single Stranded Conformation Polymorphism (SSCP) analysis; and

(d) detecting the presence or absence of Arthrogryposis Multiplex Congenita.

40. (Twice Amended) A method of detecting the presence in a human patient of an altered Survival Motor Neuron (SMN) gene associated with Spinal Muscular Atrophy, comprising:

analyzing exon 7 or exon 8 of a gene identified as T-BCD541 (SEQ ID No: ~~21~~22) in a biological sample derived from the patient, and

comparing said exon 7 ~~or exon 8~~ to the corresponding exon from nucleotide position 340 to nucleotide position 401 of SEQ ID No:13, or exon 8 to the corresponding exon from nucleotide position 846 to nucleotide position 1408 of SEQ ID No:13, which is present in a normal tissue;

wherein an alteration of either exon 7 or exon 8 in said patient sample with reference to said normal tissue is indicative of the presence of an altered Survival Motor Neuron (SMN) gene associated with Spinal Muscular Atrophy in said patient.

43. (Once amended) The method ~~of either~~ of claim 40, wherein said analyzing includes amplifying all or part of the T-BCD541 gene.

50. (Twice Amended) A method of confirming a clinical diagnosis of Arthrogryposis Multiplex Congenita in a patient, comprising

analyzing exon 7 or exon 8 of a gene identified as T-BCD541 (SEQ ID No : ~~21~~22) in a biological sample derived from the patient, and

comparing said exon 7 ~~or exon 8~~ to the corresponding exon from nucleotide position 340 to nucleotide position 401 of SEQ ID No:13, or exon 8 to the corresponding exon from nucleotide position 846 to nucleotide position 1408 of SEQ ID No:13, which is present in a normal tissue;

wherein an alteration of either exon 7 or exon 8 in said patient sample with reference to said normal tissue is indicative of the presence of an altered Survival Motor Neuron (SMN) gene associated with Arthrogryposis Multiplex Congenita in said patient.

53. (Once amended) A kit for the *in vitro* detection of a defect in the Survival Motor Neuron gene, wherein said kit comprises a probe which comprises at least 9 nucleotides within a sequence of SEQ ID No: ~~21~~22 or hybridizes under stringent conditions with a sequence of SEQ ID Nos: 1, 2, 10-13, or ~~21~~22.

54. (Once amended) A method of identifying the presence or absence of a mutation in the Survival Motor Neuron (SMN) gene in a subject, comprising

(a) isolating a nucleic acid from the subject;

(b) subjecting the nucleic acid to digestion by a restriction endonuclease, wherein restriction fragments resulting from said digestion of a mutated SMN gene differ from those obtained from a T-BCD541 gene of SEQ ID No:~~21~~22; and

(c) identifying the presence or absence of a mutation in the SMN gene in the subject.

57. (Once amended) The method of claim 56, wherein said polymerase chain reaction is performed with a set of primers which are contained in the sequence comprising nucleotides 921 to 1469 of SEQ ID No: 12, or which comprise a sequence selected from SEQ ID Nos: 5 to 8 and 24 to 57.

58. (Once amended) A method of identifying the presence of Spinal Muscular Atrophy (SMA) in a subject, said method comprising:

(a) isolating a nucleic acid from a subject; and

(b) identifying a mutation in a T-BCD541 gene (SEQ ID No: ~~2~~122);

wherein the presence of a mutation in the T-BCD541 gene is indicative of the presence of SMA in said subject.

59. (Once amended) The method of claim 58, wherein the mutation is a deletion in the T-BCD541 gene (SEQ ID No: ~~2~~122).

60. (Once amended) The method of claim 59, wherein the deletion comprises a deletion of the entire T-BCD541 gene (SEQ ID No: ~~2~~122).

64. (Once amended) A kit for the *in vitro* detection of a defect in the survival motor neuron gene, comprising:

a set of primers wherein ~~at least one of~~ said primers comprises a sequence selected from SEQ ID Nos: 5 to 8 and 24 to 57;

reagents for an amplification reaction; and

a probe for the detection of the amplified product.

65. (Once amended) A method for detecting a defect in the Survival Motor Neuron gene, said method comprising :

(a) extracting DNA from a patient sample;

(b) amplifying said DNA with primers, wherein ~~at least one of~~ said primers comprises a sequence selected from SEQ ID Nos: 5 to 8 and 24 to 57;

(c) subjecting said amplified DNA to a Single-Strand Conformation Polymorphism (SSCP); and

(d) detecting the presence or absence of said defect in the Survival Motor Neuron gene, wherein the presence of said defect is indicative of a Survival Motor Neuron disorder.